Claims

What is claimed is:

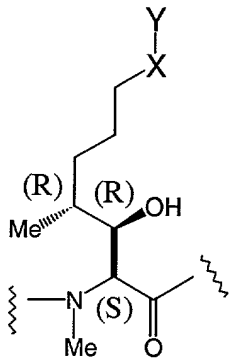
1. A cyclosporin analog of formula (I) or a pro-drug or a pharmaceutically acceptable salt thereof:

A---B---Sar-MeLeu-Val-MeLeu-Ala---U---MeLeu-MeLeu-MeVal
1 2 8

(I)

wherein,

(a) A is of the formula:



wherein

X is absent, -C1-C6 alkyl-, or –C3-C6 cycloalkyl-;

Y is selected from the group consisting of:

i. -C(O)-O-R1 where R1 is hydrogen, C1-C6 alkyl optionally substituted with halogen, heterocyclics, aryl, C1-C6 alkoxy or C1-C6 alkylthio, halogen substituted C1-C6 alkoxy, halogen substituted C1-C6 alkylthio;

ii. -C(O)-S-R1 where R1 is hydrogen, C1-C6 alkyl optionally substituted with halogen, heterocyclics, aryl, C1-C6 alkoxy or C1-C6 alkylthio, halogen substituted C1-C6 alkoxy, halogen substituted C1-C6 alkylthio;

iii. -C(O)-OCH_2-OC(O)R2 where R2 is C1-C6 alkyl, optionally substituted with halogen, C1-C6 alkoxy, C1-C6 alkylthio, heterocyclics or aryl;

iv. -C(S)-O-R1 where R1 is hydrogen, C1-C6 alkyl optionally substituted with halogen, heterocyclics, aryl, C1-C6 alkoxy or C1-C6 alkylthio, halogen substituted C1-C6 alkoxy, halogen substituted C1-C6 alkylthio; and

v. C(S)-S-R1 where R1 is hydrogen, C1-C6 alkyl optionally substituted with halogen, heterocyclics, aryl, C1-C6 alkoxy or C1-C6 alkylthio, halogen substituted C1-C6 alkoxy, halogen substituted C1-C6 alkylthio.

(b) B is –αAbu-, -Val-, -Thr- or –Nva-; and

(c) U is –(D)Ala-, -(D)Ser- or –[O-(2-hydroxyethyl)(D)Ser]-; or -[O-acyl(D)Ser]- or –[O-(2-acyloxyethyl)(D)Ser]-.

2. A cyclosporin analog according to Claim 1 or a pro-drug or a pharmaceutically acceptable salt thereof, wherein in formula (I), B is -αAbu-, and U is -(D)Ala-.

3. A cyclosporin analog according to Claim 1 or a pro-drug or a pharmaceutically acceptable salt thereof, wherein in formula I:

(i) A is of the formula A1 or A2, wherein:

X is absent; and

Y is selected from a group consisting of:

i. -C(O)-O-R1 where R1 is hydrogen, C1-C6 alkyl optionally substituted with halogen, heterocyclics, aryl, C1-C6 alkoxy or C1-C6 alkylthio, halogen substituted C1-C6 alkoxy, halogen substituted C1-C6 alkylthio;

ii. -C(O)-S-R1 where R1 is hydrogen, C1-C6 alkyl optionally substituted with halogen, heterocyclics, aryl, C1-C6 alkoxy or C1-C6 alkylthio, halogen substituted C1-C6 alkoxy, halogen substituted C1-C6 alkylthio; and

iii. $C(O)-OCH_2-OC(O)R2$ where R2 is C1-C6 alkyl optionally substituted with halogen, C1-C6 alkoxy, C1-C6 alkylthio, heterocyclics or aryl;

(ii) B is -αAbu-; and

(iii) U is -(D)Ala-.

4. A cyclosporin analog according to claim 1 or a pro-drug or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = $-COOCH_3$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = -COOH;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = -COOEt;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = $-COOCH_2CH_2CH_3$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = $-COOCH_2Ph$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = $-COOCH_2F$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = $-COOCHF_2$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = $-COOCF_3$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = $-COOCH_2CF_3$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = $-COOCH_2Cl$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = $-COOCH_2OCH_3$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = $-COOCH_2OCH_2CH_2O\ CH_3$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = $-C(=O)SCH_2Ph$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is -$CH_2CH_2CH_2$-, Y = $-COOCH_3$; and

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = -COOFmoc.

5. A chemical process for preparing a cyclosporin analog of formula I as claimed in Claim 1, comprising:
   a. reacting a compound of formula I, wherein A= -MeBmt- with:
      i. an olefin of formula CH_2=CH-X-Y, wherein X and Y are as defined in Claim 1; and
      ii. a catalyst;
      in the presence of a lithium salt in an organic solvent; and
   b. hydrogenating the product of step a in an organic solvent under hydrogen with a catalyst;
      and optionally converting the product of said reaction into a pharmaceutically acceptable salt.

6. The chemical process as claimed in Claim 5, wherein the catalyst in step (a) (ii) is Grubb's ruthenium alkylidene, Nolan's catalyst, a benzylidene catalyst or a molybdenum catalyst.

7. The chemical process as claimed in Claim 5, wherein step (b) is performed at room temperature.

8. The chemical process as claimed in Claim 7, wherein the catalyst in step (b) is Palladium on carbon.

9. A pharmaceutical composition, said composition comprising at least one cyclosporin analog of formula 1 as claimed in Claim 1, said cyclosporin analog being present alone or in combination with a pharmaceutically acceptable carrier or excipient.

10. A method for treating diseases characterized by airflow obstruction in a subject in need of treatment which comprises the step of administering to said subject a therapeutically effective amount of at least one cyclosporin analog of formula I as claimed in Claim 1.

11. The method of Claim 10, wherein said disease is asthma.

12. The method of Claim 10, wherein the step of administering the cyclosporin analog of formula I is done by topical administration.